PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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MADDERNS
26 NOV 2003

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	25 NOV 2003
REPLY DUE	within **TWO MONTHS** from the above date of mailing

Applicant's or agent's file reference	International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
21475	**PCT/AU03/00266**	3 March 2003	1 March 2002

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] G01N 33/15, 33/92; A61K 35/12, 45/06; C12Q 01/00; A61P 29/00

Applicant
WOMEN'S AND CHILDREN'S HOSPITAL et al

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[X]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The **FINAL DATE** by which the international preliminary examination report must be established according to Rule 69.2 is:
1 July 2004
4. The applicant is hereby **invited to reply** to this opinion.

When? See the **Reply Due** date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the **Final Date** by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established.
If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least **3 months before the Final Date** by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**JULIE GALE** Telephone No. (02) 6283 2272

WRITTEN OPINION

International application No.
PCT/AU03/00266

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

WRITTEN OPINION

International application No.
PCT/AU03/00266

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

The International Searching Authority found that there were multiple inventions and restricted the search to the invention as claimed in claims 1-15.

The claims of the Application are not linked by a special technical feature which is common to all independent claims nor is there evidence that the claims relate to the same inventive concept. A technical relationship (as defined in PCT Rule 13.2) does not exist.

The following inventions were found to exist:

1. Claims 1-15 relate to assays for grading a substance so as to assess its anti-inflammatory activity. The assay can be either an *in vivo* screening assay or an *in vitro* screening assay. The assay as a whole can be regarded as representing a **first "special technical feature"**.

2. Claims 16-20 relate to a pharmaceutical composition comprising emu oil or a biologically active extract or component thereof. As emu oil is well known, there is no "special technical feature" in claim 16 which could distinguish the composition from the prior art.

Claims 21-25 relate to a method of treating or ameliorating the symptoms of a T-cell mediated disease or a neutrophil mediated disease in a mammal by administering emu oil. Claims 30 and 31 relate to the preparation of emu oil by heating the oil to a temperature of at least 40°C. **A second "special technical feature"** can be regarded as the preparation of emu oil for therapeutic use and a method of therapeutic use of emu oil.

3. Claims 26*-29 relate to the use of an organic solvent to extract compounds having anti-inflammatory activity from a biologically active oil or fat wherein the organic solvent may be an alcohol. This represents a **third "special technical feature"**.

* The International Searching Authority regarded claim 26 to be unsearchable. The scope of this particular claim is so broad that any search would be uneconomic. The claim encompasses the use of any organic solvent to extract compounds from any biologically active oil or fat, the extracted compounds having an anti-inflammatory property.

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. **1-15**

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **9-13, 15**	**YES**
	Claims **1-8, 14**	**NO**
Inventive step (IS)	Claims	**YES**
	Claims **1-15**	**NO**
Industrial applicability (IA)	Claims **1-15**	**YES**
	Claims	**NO**

2. Citations and explanations

The International Searching Authority raised the issue of a lack of unity. The Applicant declined to pay additional fees. As no International Search is available for claims 16-31, no meaningful opinion can be given.

Therefore only claims 1-15 are the subject of this International Preliminary Examination.

Claims 1-15 relate to either an *in vivo* or an *in vitro* assay system for grading a substance to assess, in a standardized manner, its antiinflammatory activity.

The following documents were regarded as relevant in the ISR:

D1: Winter CA et al. (1962)

D2: Snowden JM and Whitehouse MW (1997)

D3: Hart PH et al. (2000)

D4: Lopez A et al. (1999)

D5: Whitehouse MW et al. (1998)

D6: Asuzu IU et al. (1999)

D7: WO 92/08470

D8: US 6,346,278

The relevance of each of these documents will be discussed with regard to the novelty of claims 1-15 below:

D1: This document discloses the carrageenin-induced edema in the hind paw of the rat as an assay for antiinflammatory drugs. The drugs are administered by gastric gavage an hour prior to injection of carrageenin in the foot. Swelling was then measured. This citation anticipates claims 1, 6-8 and 14 for novelty.

D2: This document discloses the study of the antiinflammatory activities of 5 different preparations of emu oil. M. tuberculosis in squaline as adjuvant was injected into the tail base of rats. Mixtures of emu oil/olive oil/cineole were applied topically to the ear. Rear paw diameters (swelling) were measured. Dose-response was then assessed. Ibuprofen, a well known anti-inflammatory, was tested. This document anticipates claims 1, 3-6, 8 and 14 of the current application.

D3: This document discloses the evaluation of potential anti-inflammatory properties of tea tree oil by examining the ability of tea tree oil to reduce the production in vitro of TNFα, IL-1β, IL-8, IL-10 and PGE_2 by LPS-stimulated human peripheral blood monocytes. These cells were used as a model for tissue macrophages. This document anticipates claims 2, 3, 4 and 14.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

D4: This document reports that topically applied emu oil reduces the severity of acute auricular inflammation induced by croton oil in mice. Both croton oil (as antigen) and emu oil were applied topically. Swelling was reduced with emu oil treatment. This document anticipates claims 1, 3-6, 8 and 14.

D5: This document discloses the measurement of paw swelling during the study of the anti-inflammatory properties of emu oil. It indicates that emu oil has trans-dermal anti-inflammatory activity. Other oils were tested including flax/linseed and evening primrose. This document anticipates claims 1, 3-6 and 8.

D6: This document discloses the application of croton oil (as antigen) to the surface of the ear to induce inflammation. Test substances were applied. The anti-inflammatory response was evaluated as percentage edema reduction. Also disclosed is an assay involving carrageenan-induced paw edema in rats. This citation anticipates claims 1, 3-8 and 14.

D7: This document discloses an anti-inflammatory composition derived from emu oil. Emu oil is administered topically, systemically and orally. There is a disclosure (see in particular Table 1 page 17) of rat oedema induced by tail base injection of M. tuberculosis in squaline followed by the topical application of oil and measurement of rear paw swelling. This document anticipates claims 1, 3-6 and 8.

D8: This document relates to the anti-inflammatory activity of a lipid-extract of mussels. Various modes of administration are discussed. Both an anti-inflammatory assay and an anti-arthritic assay are disclosed. This document anticipates claims 1, 3-8.

Observations on INVENTIVE STEP: Claims 1-15

In addition to the lack of novelty and inventiveness for claims 1-8 and 14, 15, the following observations are made on claims 3-5, 7, 14 and 15 in regard to the documents D1-D8.

D1: Claims 3-5 and 15 are objected to as lacking an inventive step as the features defined in these claims are considered in light of the common general knowledge as mere alternatives or choices for a person skilled in the art and are therefore not inventive.

D2: Claims 7 and 15 are not considered to be inventive for similar reasons as above.

D3: Claims 5, 9-13 and 15 are not considered to be inventive for similar reasons as above.

D4: Claims 7 and 15 are not considered to be inventive for similar reasons as above.

D5: Claims 7, 14 and 15 are not considered to be inventive for similar reasons as above.

D6: Claim 15 is not considered to be inventive for similar reasons as above.

D7: Claims 7, 14 and 15 are not considered to be inventive for similar reasons as above.

D8: Claims 5, 14 and 15 are not considered to be inventive for similar reasons as above.

Further to the above observations on inventive step above, claim 2 and appended claims are not considered to be inventive in view of the problem to be solved and the common general knowledge in this particular art.

The Applicant has disclosed an assay for the measurement of anti-inflammatory effects of substances. Therefore, the problem may be viewed as providing a means for assessing the anti-inflammatory activity of a substance.

The Applicant has demonstrated that an *in vitro* assay can be used to assess the anti-inflammatory activity of a substance wherein the test substance is added to an *in vitro* preparation of T-cells, macrophages or neutrophils. The activity of such cells is then observed and compared to the activity observed for a standard compound.

It is to be first noted that the comparison of a test substance against a known substance is standard practise in assays. For example, a standard curve may be generated and the activity of a test substance is then compared. Thus part (iv) of claim 2 cannot be considered to contribute an inventive step.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V: Inventive Step Observations

The person skilled in the art in relation to this current application would be someone with experience/knowledge of assay methodologies and would have an understanding of the inflammation process.

The use of cell culture as a means for assaying is well known and there are many examples of its use in the art (such as for toxicity testing of substances, monitoring the effects of test substances etc...). With particular attention to investigations of anti-inflammatory properties, it appears to be well known in the art to utilise certain cells which are known to be involved in the process of inflammation. Such cells involved in the anti-inflammatory process include macrophages, T-cells and neutrophils. For example, the literature regarding investigations of anti-inflammatory properties appears to be replete with disclosures concerning (a) the adhesion of neutrophils; (b) the use of LPS-induced macrophages and monitoring of TNF-α; (c) T lymphocyte proliferation *in vitro;* (d) chemotaxis involving neutrophils.

Therefore a claim to an assay involving the measurement of activity of an *in vitro* preparation of T-cells, macrophages or neutrophils is not regarded as demonstrating an inventive step in light of the common general knowledge. It is well known that such cells as macrophages, T lymphocytes and neutrophils are involved in the inflammation process. To then utilise these cells *in vitro* for the observation of anti-inflammatory properties of test substances cannot be regarded as demonstrating any inventiveness over and above what appears to be common general knowledge in this particular art.

In light of the above comments, claims 9-13 are also not considered to demonstrate an inventive step. A person skilled in this particular art who is acknowledged to have some understanding of the inflammation process would, without recourse to inventive faculty, arrive at the solution as defined in these claims. As stated above, it would seem to be well known to observe the proliferation of T cells as it relates to inflammatory processes (claim 9). The production of cytokines by T cells in the inflammation process is also well known, hence observations on the production of certain cytokines as indicators of anti-inflammatory activity cannot be regarded as inventive (claims 10 and 11).

INDUSTRIAL APPLICABILITY: This is acknowledged for claims 1-15.

WRITTEN OPINION

International application No.
PCT/AU03/00266

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 2003/0031724	13/02/2003	16/05/2001	16/05/2001

This document discloses anti-inflammatory compositions including those derived from emu oil. Example 1 (page 6) includes disclosure of an assay utilising the application of croton oil followed by emu oil to the inner surface of the ear of a mouse. Auricular thickness (ie degree of swelling) was observed. This citation would have particular relevance with regard to anticipating claims 1 and 3-8.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*